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Glycemic Control and Type 1 Diabetes Mellitus: Current Standard Treatment vs. Closed-Loop Insulin Pumps

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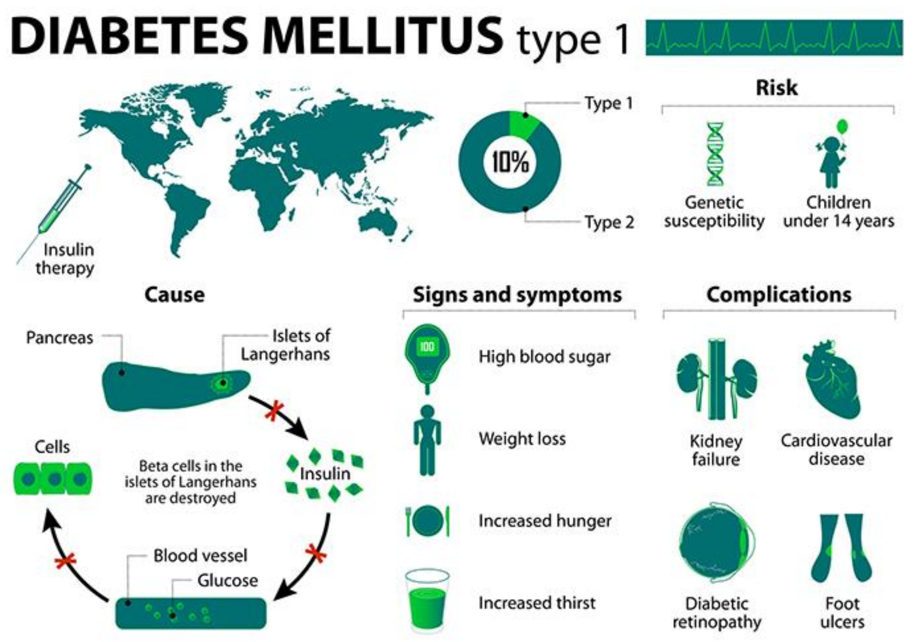
Abstract

- As of 2015, 9.4% of the US population had a diagnosis of Diabetes Mellitus (DM). Although most of the data sets studied encompass type 1 (T1) and type 2 (T2) DM data in all ages of patients, the focus of this project will be on T1DM.
- There are effective methods currently available for the management of T1DM patients. These methods include: closed-loop insulin pumps that integrate a continuous glucose monitor (CGM) and insulin pump into one effective system that calculates the needed insulin doses through complicated algorithms, CGM with self-blood glucose monitoring calibrations (SBGM) and insulin administration, and SBGM with insulin administration.
- Literature reveals that closed-loop insulin pumps have the potential to provide better disease management and improved disease outcomes for those patients who are motivated to use them as directed and find them a desirable option.
- When patients can effectively manage their blood glucose, and practice healthy lifestyle and dietary choices, they can avoid unnecessary hospitalizations and long-term diabetic complications. This will simultaneously reduce healthcare-related costs, increase longevity and can improve the patient's quality of life.

Introduction

- According to the CDC, DM affects 30.3 million people in the US. Five percent of those cases are estimated to be Type 1 Diabetes Mellitus (T1DM), and the incidence of DM is steadily increasing with an estimated 1.5 million new cases of diabetes diagnosed in 2015 alone.



Diabetes Mellitus type 1. (2016). [Graphic illustration from The Natural Society August 28, 2016]. *The Natural Society*. Retrieved from http://naturalsociety.com/wp-content/uploads/diabetes-mellitus-chart-full.jpg

Statement of the Problem

- Current medical treatment for diabetic patients require self-blood glucose monitoring, this monitoring is done using self-blood glucose monitors (SBGM), which results in many finger sticks.
- Insulin injections can be performed by the patient or by an insulin pump that must be manually programmed, which requires the patient to be proficient calculating insulin doses independently. There is a high potential for error related to insulin administration due to incorrect calibration of the glucometer or basic human error.
- When patients practice good blood glucose management they can avoid unnecessary hospitalizations and other diabetic complications, which will simultaneously reduce healthcare-related costs. These choices should be based on scientific evidence of effectiveness, not unreliable reports and should be made after considering the patient's lifestyle and its' impact on each method's particular benefits and challenges.
- The CDC (2017) states that In 2014, a total of 7.2 million hospital discharges and 14.2 million emergency department visits were reported with diabetes being listed as any kind of diagnosis among US adults aged 18 years or older. The total direct and indirect estimated cost of diagnosed diabetes in the US in 2012 was $245 billion; with an average of $13,700/year/person being medical expenditures related to diabetes. This is around 2.3 times higher than expenditures for people without diabetes. It is also important to note that DM was the seventh leading cause of death in the US in 2015.

Research Questions

- Will closed-loop insulin pumps provide better efficacy by monitoring glycemic control according to patient's blood glucose levels and glycosylated hemoglobin levels (HgbA1C) and decrease the incidence of hypoglycemic episodes, as compared to the current standard treatment of insulin pump therapy in patients with T1DM?
- What are the unique benefits of the different effective T1DM management methods?
- What are the challenges of these management methods and how will they affect their actual use-effectiveness?

Literature Review

- The DCCT performed by Nathan, D. M., Bayless, M., Cleary, P., Glenuth, S., Gubitosi-Klug, R., Lachin, J. M., ... Zinman, B. (2013)showed an improvement in the INT group with the following outcomes: **HgbA1C** - by three to six months to a level of 6.9% from the initial 9.1% . **Microvascular** – results found were consistent, significant, and clinically meaningful. **Cardiovascular** – the patient population was generally too young and healthy to experience major CVD events (p= 0.059) INT group with three events in three subjects vs. CONV with twenty-one events in nine subjects. **Beta cell preservation** – INT group slowed the rate of loss of C-peptide responsiveness by ~50%.
- Devries (2017) reports results from a randomized crossover trial comparing day-and-night closed-loop insulin delivery with usual pump therapy (four weeks each) in 29 adults with well controlled T1DM (HgbA1C <7.5%). A closed-loop system was used, in which the participant determined the amount of insulin administered before each meal. Participants had sensor glucose concentration in target range (3.9–10.0 mmol/L) 65.6% (SD 8.1) of the time during usual pump therapy and 76.2% (SD 6.4) of the time during closed-loop delivery which showed that the closed-loop system increased the proportion of time when glucose concentration was in target range by 10.5 percentage points (95% CI 7.6–13.4; p<0.001). Compared with usual pump therapy, closed-loop delivery reduced mean glucose concentration by 0.4 mmol/L (0.1–0.7, p=0.0226); the proportion of time with glucose concentration above 10.0 mmol/L by 6.9 percentage points (3.5–10.2; p=0.0003) and below 3.9 mmol/L by 50% (37–59, p<0.001); and glycemic dispersion (ie, SD of glucose concentration) by 0.5 mmol/L (0.3–0.7, p<0.001).

Common Risk Factors for Diabetic Complications	
2011-2014, US adults >18 years of age with diagnosed diabetes, [95% CI]	
Smoking	15.9% were current smokers and 34.5% had quit smoking but had a history of smoking at least 100 cigarettes in their lifetime.
BMI	87.5% were overweight or obese, defined as a BMI of 25 or greater; 26.1% having a BMI of 25-30, 43.5% having a BMI of 30-40, and 17.8% with a BMI of 40 or higher.
Physical Inactivity	40.8% of adults got less than 10 minutes/week of moderate to vigorous activity in either work, leisure, or transportation.
Hypertension	73.6% had systolic BP of 140mmHg or higher and diastolic BP of 90mmHg or higher, or they were already on BP controlling medications.
High Cholesterol	58.2% over age 21 with no self-reported CV disease who were eligible for statin therapy and were on a lipid-lowering medication. 66.9% over age 21 with self-reported CV disease who were eligible for statin therapy and were on a lipid-lowering medication.
Hyperglycemia	15.6% of adults had a HgbA1C value higher than 9%.

Center for Disease Control and Prevention. (2017). *The National Diabetes Statistics Report* [Data file]. Retrieved from https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf

Discussion

- Historical studies show that an intensive insulin regimen along with strict monitoring of blood glucose and HgbA1C levels provide patients with less long-term microvascular side effects of retinopathy, neuropathy, and nephropathy, as well as the macrovascular side effects of cardiovascular, peripheral vascular and cerebrovascular disease.
- The DCCT performed by Nathan, et al. (2013) demonstrated a drop of nearly ~2.5% in HgbA1C and a slowed rate of loss in C-peptide responsiveness in Beta cell preservation. The EDIC performed by Nathan, et al. (2013) demonstrated the need for earlier intervention in T1DM by showing that it can reduce severe renal impairment by ~50%, risk of primary CVD outcomes by 42%, and nonfatal MI or stroke by 58%.

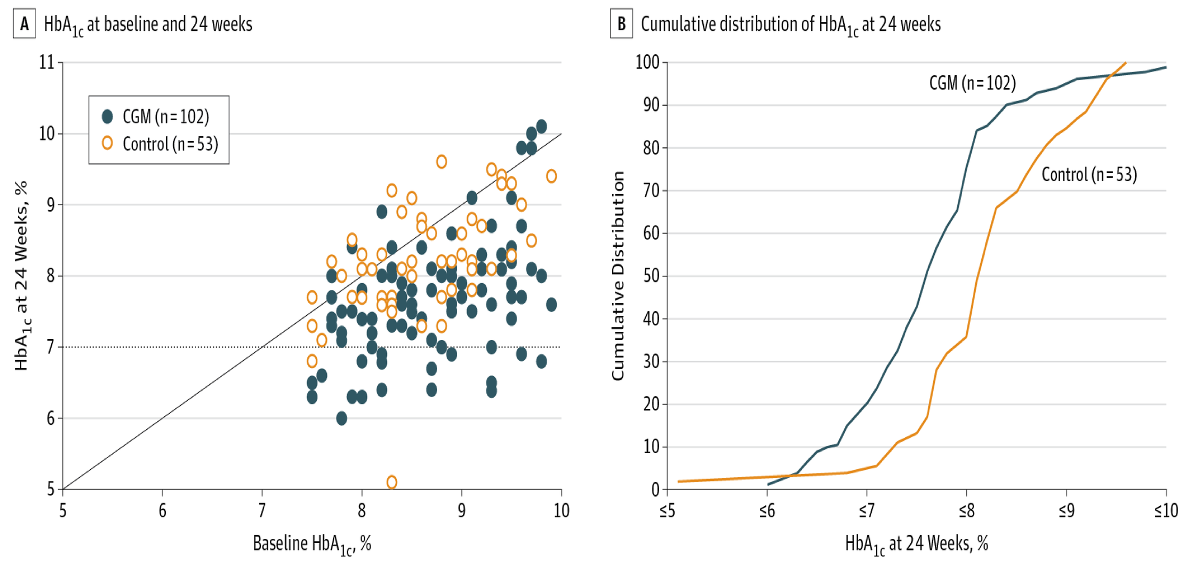


Table adapted from Beck, et al, 2017 https://doi.org/doi:10.1001/jama.2016.19975

Overview of Randomized Controlled Trails on Use of Closed loop in type 1 diabetes by years (CL – closed loop; SAP – sensor augmented pump: any insulin pump coupled with any sensor for continuous glucose monitoring).

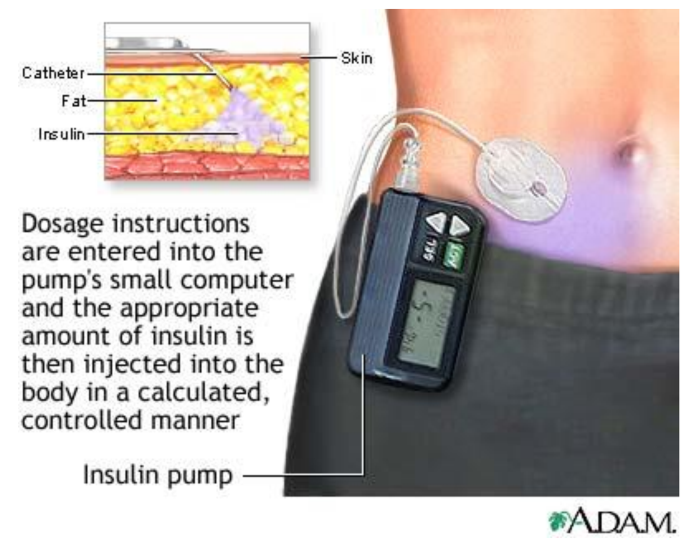
Year	Study author (reference number)	Number of patients	Mean age	Study duration	Intervention	Primary study end point	Outcome: intervention vs control
2010	Hovorka [33]	21	13.5	2–5 days	CL vs SAP	Time in target glycaemic range; time in hypoglycaemia	20% ($p = 0.00225$); −2 ($p = 0.0304$)
2011	Hovorka [40]	24	37.5	2–7 days	CL vs SAP	Time in target glycaemic range	15% ($p = 0.002$, eating in); 28% ($p = 0.01$, eating out)
2011	Murphy [54]	12	32.9	48 h	CL vs SAP	Time in target glycaemic range; time in hypoglycaemia	81% vs 81% ($p = 0.75$); 0.0 vs 0.03 ($p = 0.04$)
2012	Breton [41]	38	41 (adults), 14.5 (adolescent)	22 h	CL vs SAP	Time in near normoglycaemia, time in tight glycaemic range, time in hypoglycaemia	12.9% ($p = 0.01$), −2.5% ($p = 0.66$), −2.7 ($p = 0.01$)
2013	Haidar [31]	15	/	30 h	Dual-hormone CL vs SAP	Time in target glycaemic range; time in hypoglycaemia	13.4% ($p = 0.003$), 10.2% ($p = 0.01$)
2013	Elleri [38]	12	15.0	36 h	CL vs SAP	Time in target glycaemic range, mean plasma glucose level	35% ($p = 0.02$), −37 mg/dl ($p = 0.02$)
2013	Sherr [37]	12	16.8	96 h	CL vs SAP	Night hypoglycaemia, time in target glycaemic range	−2.5% (sedentary), −6% (exercise) ($p = 0.04$), 30% (sedentary), 14% (exercise) ($p < 0.0001$)
2013	Schmidt [42]	6	45	2 nights	CL vs SAP	Time in target glycaemic range, mean glucose, hypoglycaemic events	12.9% ($p = 0.08$), 18 mg/dl ($p = 0.38$), −3.7% ($p = 0.22$)
2013	Philip [39]	56	13.8	2 nights	CL vs SAP	Number of hypoglycaemic events, time spent in hypoglycaemia, mean overnight glucose level, time in target range	−15 ($p = 0.003$), 0 ($p = 0.02$), −14 mg/dl, 1.4 ($p < 0.05$)
2013	Nimri [47]	15	19	8 nights	CL vs SAP	Time in hypoglycaemia, percentage of nights with mean glucose in target range	−44.9 min ($p = 0.0034$), 17% ($p = 0.5692$)
2013	Luijf [48]	48	41.5	72 h	CL vs SAP	Time in target glycaemic range, mean glucose level, time in hypoglycaemia	−5.3% ($p = 0.377$), −4.3% ($p = 0.001$), 18 mg/dl ($p = 0.001$)
2013	Dauber [36]	10	5.1	2 nights	CL vs SAP	Time in target glycaemic range, time in hypoglycaemia	2.1 h ($p = 0.12$), −0.04 h ($p = 0.86$)
2014	Capel [43]	10	46.7	2 nights	CL vs SAP	Time in target glycaemic range, time in hypoglycaemia	29.5% ($p < 0.05$), −4.2% ($p < 0.05$)
2014	Hovorka [46]	16	/	6 weeks	CL vs SAP	Time in target glycaemic range, mean overnight glucose, time in hypoglycaemia	15% ($p < 0.001$), −14 mg/dl ($p < 0.001$), −7% ($p < 0.01$)
2014	Kovatchev [49]	20	/	80 h	CL vs SAP	Time in target glycaemic range, LGBI, hypoglycaemic events, mean BG, time in hypoglycaemia	−4.6% ($p > 0.1$), 0.64 ($p = 0.003$), 1.2 ($p < 0.02$), 9 mg/dl ($p < 0.04$), −0.55% ($p > 0.1$)
2014	Leelarathna [50]	17	34	16 days	CL vs SAP	Time in target range, mean BG, time spent in hypoglycaemia	13% ($p = 0.005$), −12.6 mg/dl ($p = 0.027$), −1.3% ($p = 0.339$)
2014	Ly [35]	20	/	106 nights	CL vs SAP	Time in target glycaemic range	7% ($p = 0.233$)
2014	Nimri [44]	24	28.6	2 nights	CL vs SAP	Time in hypoglycaemia, time in target glycaemic range	−2.13% ($p = 0.02$), 10.95% ($p = 0.003$)
2014	Oron [34]	37	12.4	2 weeks	CL vs SAP	Nocturnal hypoglycaemia episodes, time in target range	−2.8% ($p = 0.443$), 4.8% ($p = 0.207$)
2014	Russell [51]	52	40 (adults), 16 (adolescents)	5 days	Bihormonal Cl vs SAP	Mean plasma glucose level; time in hypoglycaemia	−26 mg/dl (adults, $p < 0.001$), −16 mg/dl (adolescent, $p = 0.004$); −3.2% (adults, $p = 0.01$), −1.8% (adolescents, $p = 0.05$)
2014	Thabit [45]	25	43	11–12 weeks	CL vs SAP	Time in target glycaemic range	6.4% ($p = 0.0016$)

CL, closed loop; SAP, sensor augmented insulin pump.

Table adapted from Battelino, Omladic, and Phillip 2015 from https://doi.org/10.1016/j.beem.2015.03.001

Applicability to Clinical Practice

- Initial management of a T1DM patient should include basic disease education, demonstration of SBGM, insulin administration, how to recognize and treat a hypoglycemic episode, and how to measure either blood or urine ketone concentration. This will require a multidisciplinary team that should ideally include an endocrinologist, a certified nurse educator, dietitian, and possibly a mental-health professional to provide support if the need should arise.
- As potential future family practice providers, we must consider our patient's lifestyle, education level, cognition, desire for disease control, and socioeconomic status to adequately make a choice for their T1DM management regimen.
- SBGM and insulin injections are relatively inexpensive, whereas newer technology is initially more expensive, but provide better efficacy and ease of use and also a decrease in hypoglycemic events and hospitalizations. Clinicians must be mindful of what type of insulin delivery system that they are recommending for each patient.
- Closed-loop systems have proven themselves effective; and can lessen disease burden on the patient's lifestyle. They are appropriate to prescribe for use in patients that can manage them efficiently and are motivated to do so. Closed-loop systems should be strongly considered as a long-term management method in patients with T1DM.



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